Medical and Pediatric Oncology 26:220–222 (1996)

Interferon-Alpha for Neurofibromas

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A twelve-year-old female with neurofibromatosis, presenting with plexiform neurofibromas causing severe pain and in whom relief of pain was achieved after administration of interferon-alpha, is presented.

Key words: neurofibroma, neurofibromatosis, interferon-alpha

INTRODUCTION

Neurofibromatosis type-1 (NF-1), also known as von Recklinghausen's disease, is a multifocal neurocutaneous disease affecting 1 of 3,000 people [1,2]. Currently, no laboratory evaluation can unequivocally confirm the diagnosis of NF. In 1987, a consensus committee formed by the National Institutes of Health, defined seven diagnostic criteria, two of which are required to make a definitive diagnosis of NF-1 [3]. Café-au-lait lesions and neurofibromas are cutaneous findings of NF-1 [1–4]. Neurofibromas are benign neurogenic tumors, arising from peripheral nerves. Although usually asymptomatic, neurofibromas occasionally cause pain or progressive loss of function from nerve compression. Various treatment modalities are considered to decrease pain [1]. In this paper a case with neurofibromas causing severe pain and in whom alpha-interferon was used is reported.

CASE REPORT

A twelve-year-old white female presented with pain on the left leg in May 1991. She had light brown, flat café-au-lait lesions all over her body and a raised hyperpigmented lesion in the medial portion of the left thigh from birth. The café-au-lait spots had increased in size and number, and the raised hyperpigmented lesion had increased in size. At 5 6/12 years of age, a biopsy taken from the hyperpigmented lesion on the left thigh revealed a neurofibroma. In 1985 and 1986, a cerebral and orbital CT was taken which was found to be normal. A lung X-ray and plain films of the vertebrae revealed scoliosis. She complained from pain on the left leg. In 1987, she had used, as per her family's will, the extract of oleander orally for 4.5 months without any benefit.

On physical examination at admission, about 40 café-au-lait spots, varying from 1 mm to 10 cm in diameter, were seen all over the trunk and extremities. A $17 \times 9 \times 3.5$ cm mass on the medial left thigh and a $7 \times 4 \times 3.5$ cm mass on the lateral part of the left upper arm was observed (Fig. 1). Both were hyperpigmented, soft and gritty on palpation, and had a rough border. A biopsy taken from the mass revealed a neurofibroma. Firm, well-circumscribed, movable subcutaneous nodules were palpated on the pelvis and on the left thigh. Scoliosis was present. She had strabismus and on ophthalmological examination Lisch nodules (iris hamartomas) were observed. There was no pathology on the cranial and orbital CT and abdominal ultrasound. CT of the left upper arm, left thigh and pelvis revealed a soft tissue mass limited to the skin on the left upper arm, multiple nodular soft tissue masses in between the muscles in the left femoral region, coxofemoral region and the left pelvis. The patient was diagnosed as NF-1 according to criteria defined in the National Institutes of Health Consensus Development Conference [3].

The patient's primary complaint was severe pain on the left leg that interfered even with her sleep. The patient was followed with a multidisciplinary approach for 9 months, during which she used analgesics, with temporary relief of pain. The pain was thought to be due to nerve compression. A radiation oncology consultation was made, radiotherapy was not recommended because of the wide lesion, taking into account its late effects on a growing child. A surgical wide excision was recommended, but the family did not accept it.

The pain increased with time. The use of interferon-alpha was considered for its antiproliferative effect. By the family's written consent, interferon-alpha 3×10^6 U/day SC (Roferon A, Roche, Basel, Switzerland) was

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Received August 12, 1994; accepted December 15, 1994.

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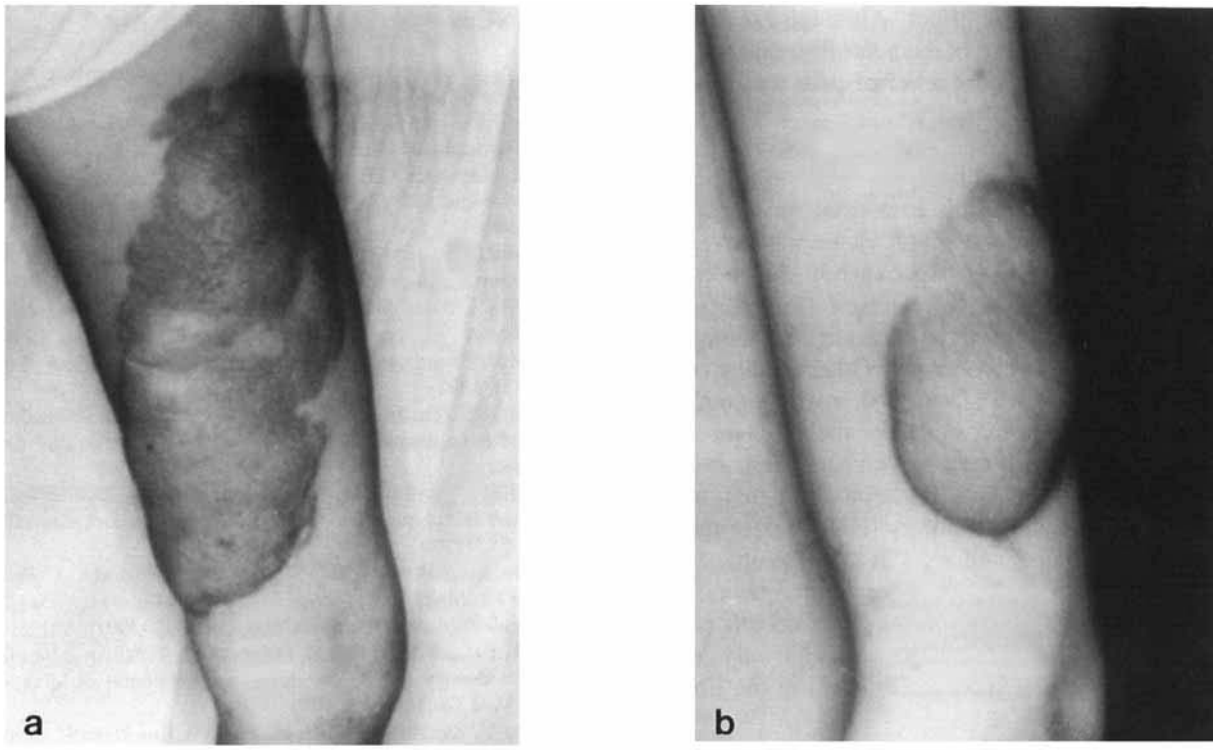

Fig. 1. Neurofibroma **(a)** on the medial left thigh; **(b)** on the lateral part of the left upper arm.

initiated thrice a week, every other day. From the second week on, the dose was escalated to 6×10^6 U/day SC thrice a week and continued for 6 months. Two weeks after the initiation of interferon-alpha, the pain began to decrease. She could sleep at night. The patient was seen every week the first month and every other week thereafter. CBC, ESR, biochemistry, ECG were normal at the beginning and during follow-up. No objective decrease in the dimensions of the mass either by physical examination or CT was seen at the end of 6 months. Thus, interferon was stopped. The patient has been followed for a further 9 months now. She has only mild pain on the left leg that does not interfere with her daily activities nor sleep. She can do without analgesics. There is no increase in the size of her neurofibromas.

DISCUSSION

Neurofibromas are benign neurogenic tumors, arising from peripheral nerves. They can be divided into two subtypes: (1) subcutaneous nodules are firm, well-circumscribed, movable tumors that are rarely painful. They can occur at any subcutaneous site along any peripheral nerve; (2) by contrast, plexiform neurofibromas are soft and gritty on palpation. They can grow to enormous proportions. These tumors are frequently tender on palpation, yet are initially painless if not manipulated; however, they can cause significant pain as they progress. The skin that covers plexiform neurofibromas is often hyperpigmented and has a rough border. Controversy exists regarding the potential for malignant transformation of a plexiform neurofibroma; nonetheless, a tumor that is growing rapidly or changing in some characteristic fashion may require biopsy. These lesions can involve or extend to visceral organs [2].

Although usually asymptomatic, neurofibromas occasionally cause pain or progressive loss of function from nerve compression. Various treatment modalities are considered to decrease pain. In our patient there were two plexiform neurofibromas, the bigger one on the thigh causing severe pain and extending into the pelvis.

At first, the pain could be relieved with analgesics. As the severe pain interfered with the child's daily activities and even sleep, other treatment modalities were considered. Radiation therapy was not given, taking into account its effect on bone and soft tissue in a growing child and the potential of malignant transformation of irradiated sites. Experimentally, as little as 200 rads of radiation on Schwann cells have well-known proliferative effects [5]. The fact that only 3–6% of neurofibromas transform spontaneously (without irradiation) should not detract from the life-threatening and treatment-resistant nature of postirradiation sarcomas as a whole and, in particular, those of nerve sheath tumors [6,7]. Radical and mutilating surgery was not accepted by the family.

Interferon-alpha usage was considered, taking into ac-

count its antiproliferative effect. Although no objective decrease in the dimensions of the neurofibromas was seen in this patient, a significant relief of pain was observed after the use of interferon-alpha. We do not know the exact mechanism of pain relief obtained in this case, but we speculate that it might be due to its antiproliferative effect. Although it was as little so as to be undetectable on CT, it might have been enough to release the nerve compression. There is growing experience using interferon-alpha for its antiproliferative effects. Case reports have been published using interferon-alpha in the treatment of life-threatening hemangiomas [8]. Other studies on the inhibition of growth of cultured meningioma and meningioma/neurofibroma cells by recombinant interferon-alpha has been reported as well [9]. There are most likely many other effects of interferon-alpha that are unknown at this time and temporary relief of pain may be merely an epiphenomena of a much more complex pathway. It is also possible that the use of experimental therapy may have had a psychological effect on this patient and the family. To our knowledge, this is the only case of interferon-alpha usage for neurofibromas in the English literature.

In conclusion, although no objective decrease in the dimensions of the neurofibromas was seen in this patient, a significant relief of pain was observed after the use of interferon-alpha for neurofibromas. Further clinical investigation is needed to support these observations.

ACKNOWLEDGMENTS

We thank Emin Darendeliler, M.D. and Sidika Kurul, M.D. for consulting the patient.

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